PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
95.80591/002		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001654	15.04.2004	15.04.2003
International Patent Classification (IPC) or national classification and IPC		
A61K51/04, A61P35/00		
Applicant		
ALGETA AS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the International application

Date of submission of the demand	Date of completion of this report
15.11.2004	17.08.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Skjöldebrand, C Telephone No. +49 89 2399-8467

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-39	as originally filed
Claims, Numbers	
1-20	received on 16.11.2004 with letter of 15.11.2004
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-13 (I.A. only)

   because:

   ☒ the said international application, or the said claims Nos. 1-13 (I.A. only) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001654

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14, 18-20
	No:	Claims	15-17
Industrial applicability (IA)	Yes:	Claims	14-20
	No:	Claims	1-13

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 2004/043487 A (BRACCO IMAGING SPA ; DE HAEEN CHRISTOPH (IT)) 27 May 2004 (2004-05-27)

D2: US 2001/008625 A1 (LARSEN ROY H ET AL) 19 July 2001 (2001-07-19)

D3: WO 01/60417 A (LARSEN ROY H ; ANTICANCER THERAPEUTIC INV S A (NO); HENRIKSEN GJERMUND) 23 August 2001 (2001-08-23)

D1: cf. Item VI below.

D2 discloses receptor conjugates with an antibody, a folate, and a radionuclide such as ^{227}Th (cf. claims 1-4) to be used in the treatment of different soft-tissue cancer forms (cf. claim 20). Kits where the radioligand and the antibody are separate are also described (cf. claims 22, 23).

D3 discloses conjugate systems comprising a liposome with a chelator, such as DOTA (cf. claim 3) and a heavy alpha-emitter such as ^{227}Th (cf. claim 12). The liposomes may be conjugated to antibodies and are useful in the treatment of various non-skeletal cancer forms (cf. claim 30). Kits where the liposomes, the radionuclide and the targeting molecule are in separate vials are disclosed (cf. claims 31, 32).

Novelty - Article 33(2) PCT

By the exclusion of liposomes, folate, antibodies etc. as recognition units in, novelty is

established over D2 and D3 for all the independent claims.

Inventive Step - Article 33(3) PCT

D2 and D3 are silent about the dosage of ^{227}Th. The high dosages as in the examples couldn't be derived from the prior art. Claims 1-14 and 18-20 appear to relate to inventive subject-matter.

An inventive step cannot be recognised for independent claims 15 and 17, as no dosage is referred to therein. The mere novelty-establishing exclusions of liposomes etc. are not sufficient to establish an inventive step over D2 and D3.

Industrial Applicability - Article 33(4) PCT

For the assessment of the present claims 1-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2004/043487	2004-05-27	2003-11-13	2002-11-14

D1 (WO 2004/043487) is an earlier filing (E-document) with a possible relevance for novelty in the European phase.

D1 discloses conjugates comprising ^{227}Th (claim 14) for the treatment of e.g. gastric tumours. The complexes have recognition units that appear to not belong to the excluded groups (bone-seekers, liposomes etc.). There is no disclosure on the dosage of the ^{227}Th.

D1 appears to interfere with novelty of independent claim 15.

Claims

1. A method for the treatment of soft tissue disease in a mammalian subject, said method comprising administering to said subject a therapeutically effective quantity of a soft tissue targeting complex of thorium-227 and a complexing agent, wherein said quantity is such that an acceptably non-myelotoxic quantity of radium-223 is generated *in vivo* by nuclear decay of the administered thorium-227 wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments and wherein the therapeutically effective quantity of thorium-227 is at least 25 kBq/kg.

2. A method as claimed in claim 1 wherein said subject is human or canine.

3. A method as claimed in any one of claims 1 to 3 wherein said therapeutically effective quantity is at least 75 kBq of thorium-227 per kilogram bodyweight.

4. A method as claimed in any of claims 1 to 3 wherein said acceptably non-myelotoxic quantity is less than 300 kBq radium-223 per kilogram bodyweight.

5. A method as claimed in claim 4 wherein said acceptably non-myelotoxic is less than 150 kBq of radium-223 per kilogram bodyweight.

6. A method as claimed in any of claims 1 to 5 wherein said complex comprises chelated thorium-227 linked to a ligand selected from the group of antibodies, antibody constructs, antibody fragments, constructs of antibody fragments and mixtures thereof.

7. A method as claimed in any of claims 1 to 6 wherein said soft tissue disease is a malignant disease.

8. A method as claimed in claim 7 wherein the malignant disease is a disease selected from the group of carcinomas, sarcomas, myelomas, lukemias, lymphomas and mixed type cancers.

9. A method as claimed in any of claims 1 to 8 wherein said subject is also treated to combat the myelotoxicity of the radium-223 generated therein.

10. A method as claimed in claim 9 wherein said subject is provided with stem cell treatment.

11 A method for the treatment of soft tissue disease in a mammalian subject, said method comprising administering to said subject a therapeutically effective quantity of a soft tissue targeting complex of thorium-227 and a complexing agent, wherein said quantity is D_{add} as calculated from formula I below, such that an acceptably non-myelotoxic quantity D_{Ra} of radium-223 is generated *in vivo* by nuclear decay of the administered thorium-227;

$$D_{add} = \frac{D_{Ra} \times T_{Th}\left((T_{Bio})^{-1} + (T_{Th})^{-1}\right)}{1.65} \qquad (I)$$

wherein:

T_{Bio} is the biological half-life of said soft tissue targeting complex of thorium-227 and a complexing agent;

T_{Th} is the physical half-life of ^{227}Th (18.7 days);

D_{add} is the activity of the administered ^{227}Th complex (kBq/kg) and is is at least 25 kBq/kg; and

D_{Ra} is the acceptably non-myelotoxic amount of ^{223}Ra;

and further, wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

12. A method as claimed in claim 11 wherein D_{Ra} is 200 kBq/kg

13. A method as claimed in any of claims 1 to 12 in combination with at least one further treatment modality selected from surgery, external beam radiation therapy, chemotherapy, endoradionuclide therapy with radionuclides other than ^{227}Th, and/or tissue temperature adjustment.

14. A pharmaceutical composition comprising a soft tissue targeting complex of thorium-227 and a complexing agent, together with at least one pharmaceutical carrier or excipient wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments and wherein the thorium-227 is present at a therapeutically effective quantity of at least 25 kBq/kg.

15. A soft tissue targeting complex of thorium-227 and a complexing agent wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

16. A complex as claimed in claim 15 wherein thorium-227 is chelated by a derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid.

17. A method for forming a complex as claimed in claim 16 comprising heating said thorium-227 with said derivative of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to form a chelated thorium-227 and subsequently attaching said chelated thorium-227 to a targeting moiety.

18. A kit for use in a method as claimed in any of claims 1 to 13, said kit comprising a solution of a soft tissue targeting complex of thorium-227 and a complexing agent together with instructions for the use of said solution in said method wherein the thorium-227 is conjugated to a targeting moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

20. A kit for use in a method as claimed in any of claims 1 to 13, said kit comprising a complexing agent capable of complexing thorium ions; where said complexing agent is not a soft tissue targeting complexing agent, a soft tissue targeting compound, optionally together with a linker compound, conjugatable to said complexing agent to yield a soft tissue targeting complexing agent; and instructions for the preparation therefrom of a soft tissue targeting complex of thorium-227 and a complexing agent, and optionally also for the use of said complex in said method wherein the soft tissue targeting complex is a moiety with bioaffinity, excluding bone-seekers, liposomes and folate conjugated antibodies or antibody fragments.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/421,244	04/23/2003	Roy H. Larsen	50147/006001	4638

21559 7590 01/12/2007

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/421,244	LARSEN ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,7 and 9-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,4,6,7 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "**said**," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

2. Claims 7 and 9 are objected to because of the following informalities: The claim language for the Markush groups of the instant claims 7 and 9 is not in the proper form. Markush group claim terminology should read as follows “selected from the group consisting of..”. Appropriate correction is required.

3. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim 6 recites “ acceptably non-myelotoxic quantity is less than 150kBq of radium-223 per kilogram bodyweight” which is broader than the “acceptably non-myelotoxic quantity of radium-

223 of at least 40kBq/kg" of the claim 1 to which it depends. Therefore the instant claim 6 is not further limiting of the independent claim 1 to which it depends.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Larsen et al. (WO02/05859A2).

6. Larsen et al. (WO02/05859A2) teaches of the method of treating a malignant soft-tissue disease (p1, lines 1-12; p9, lines 24-31) by administering to a mammalian subject (p9, lines 6-7) a ^{227}Th-chelator complex, not excluding non-liposomal radiopharmaceutical complexes (p4, line 35; p7, lines 19-24). The decay of the ^{227}Th generates in vivo an emissions cascade of α-particles, such as the daughter radionuclide ^{223}Ra that will occur in the target area (p6, lines 33-37; p11, line 12) where ^{223}Ra is the first daughter nuclide in the emissions cascade of ^{227}Th. The preparation of the ^{227}Th-chelator complex for administration may be in a pharmacologically acceptable carrier (p8, line 37). It is clearly disclosed that the ^{227}Th-chelator complex is also targeted to bone as well as bone surfaces where soft tissue, such as bone marrow is located. The ^{227}Th-chelator complex is used to irradiate the bone surface with α-particles to inactivate microscopic deposits of cancer cells on the bone surfaces (p7,

lines 33-36). It is disclosed that that the complex be preferentially distributed to the bone but it is also disclosed that the ratio of distribution of the complex to femur to liver (soft tissue) is from 3:1, 8:1 or at best 15:1, etc. (p4, lines 3-15; p15, lines 20-35). Therefore the disclosure anticipates that the 227Th-chelator complex will be targeted to soft-tissue as the authors state that they anticipate at least some soft-tissue targeting. The instant claims do not provide for any structural limitations to differentiate the radionuclide complex of the disclosure which is within the scope of soft tissue targeting radionuclide complex and also due the proximity of the bone and soft tissue, such as bone marrow. The dosages of the ^{227}Th-chelator complex of the disclosure encompass those of the instant claims and are taught to reduce myelotoxicity and therefore they would generate the acceptably non-myelotoxic quantity of the daughter radionuclide ^{223}Ra. Therefore the administration of such doses would also cause reduction of the neutrophil cell count to a nadir no less than 10% of the count prior to treatment.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1,2,4,6,7 and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larsen et al. (WO02/05859A2) in view of .

9. Larsen et al. (WO02/05859A2) discloses the method of treating a malignant soft-tissue disease (p1, lines 1-12; p9, lines 24-31) by administering to a mammalian subject (p9, lines 6-7) a ^{227}Th-chelator complex, not excluding non-liposomal radiopharmaceutical complexes as well as that listed above. Also, the method of treating a soft tissue disease includes those diseases such as cancer (i.e. myeloma, etc.) (p9, lines 24-35) and includes reducing myelotoxicity (p8, line3). The kits for the preparation of the ^{227}Th-chelator complex used for the treatment of malignant soft tissue disease include the ^{227}Th radioisotope, the radioisotope chelate and for the preparation of a solution, the pharmaceutically acceptable carrier (p10, lines 18-32). The dosage administered to a patient of the ^{227}Th-chelator complex varies between approximately 10kBq-2MBq/kg bodyweight (p10, lines 14-15). This dosage range encompasses that of the instant claims, such as 75kBq/kg and 36-200kBq/kg. Furthermore, it is obvious to vary and/or optimize the amount of (compound) provided in the composition, according to the guidance provided by (reference), to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

10. Inverardi et al. (US 2003/0228256A1) discloses the administration of a bone seeking radionuclide-ligand complex where the radionuclide may be ^{223}Ra and the ligand is an aminophosphonic acid (p3, [0033]). The radionuclide-ligand complexes can be administered to a patient in pharmaceutically acceptable dosage forms and can be

localized into bone and other tissues (p4, [0036] and [0038]). The radioactivity will remain in recipient bone thereby affecting the bone marrow or bone marrow-derived cells therein, for the life of the isotope (p4, [0037]). The patient may also be administered stem cells (p4, [0038]).

11. Goldenberg (US 6,083,477) discloses a toxin-ligand conjugate that binds to a specific cellular surface marker on a cell and its method of use for tumor therapy (column 1, lines 11-16). It is disclosed that doses of antibody and or radioactivity usually require stem cell rescue and the goal for such is to decrease myelotoxicity generated by an antibody-radionuclide composition (column 1, lines 40-47). The conjugate of the disclosure is a toxin-therapeutic radionuclide-IL-15 complex where IL-15 is a fusion protein comprising a bispecific antibody that has a specificity for a cell marker specific to a malignant cell thereby localizing the toxin-therapeutic radionuclide-IL-15 complex effectively to a desired cancer site (column 2, lines 34-38). This complex is useful for the treatment of leukemias and lymphomas (column 2, lines 40-42).

12. At the time of the invention it would have been obvious to one ordinarily skilled in the art to employ the step of stem cell therapy of as disclosed by Inverardi et al. (US 2003/0228256A1) or Goldenberg (US 6,083,477) since it is known in the art to be used in conjunction with radiotherapy. The ^{223}Ra-ligand complexes as seen by Inverardi et al. could localized into bone and other tissues as does the ^{227}Th-chelator complex of Larsen et al. (WO02/05859A2) and the radioactivity will remain affect the bone marrow or bone marrow-derived cells therein, for the life of the isotope. Therefore it would be obvious that the daughter radionuclide of the ^{227}Th-chelator complex would be

generated and at least partially localized into the soft tissue as Larsen et al. describes. The decay of the ^{227}Th generates an emissions cascade of α-particles, such as the daughter radionuclide ^{223}Ra that will occur in the target area where ^{223}Ra is the first daughter nuclide in the emissions cascade of ^{227}Th. The dose of 223-Ra is dependent on the decay properties of ^{227}Th radionuclide and since the dosage of Larsen et al. encompasses that of the instant claims, the dose of ^{223}Ra generated in vivo would be equivalent also obviously encompass that of the instant claims.

It is respectfully pointed out that instant claim 15 is a product-by-process limitation. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1,2,4,6,7 and 9-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10,18 and 19 of copending Application No. 10/552,876. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the copending application 10/552,876 are both drawn to the method for treating malignant soft tissue disease in a mammalian subject via administration of a thorium-227 conjugate comprising an antibody. Also the generation of radium-223 via administration of a thorium-227 conjugate of the copending application 10/552,876 encompasses the generation of 40kBq/kg or less than 150kBq/kg of radium-223 via administration of 36-200kBq/kg or more specifically 75kBq/kg of the thorium-227 conjugate of the instant claims. The diseases to be treated by the thorium-227 conjugate include carcinomas, sarcomas, myelomas, etc. The subjects of the instant claims and of the copending application 10/552,876 are treated with stem cells to combat the myelotoxicity of the radium-223 generated. The kits of the instant claims are encompassed by those of the copending application 10/552,876.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
January 4, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER